REMARKS

In a non-final Office Action mailed October 16, 2006, the Examiner in charge of the above-identified application objected to and rejected the claims for a variety of reasons. Applicants respond below to the issues presented in the Office Action. In view of the amendments noted above and the arguments presented herein, applicants respectfully request reconsideration of the merits of this application.

Election Restrictions

Although applicants continue to traverse the Examiner requirement for restriction, the finality of the requirement is acknowledged. Accordingly, applicants wish to reserve the right to file a divisional application drawn to the non-elected claims (Claims 1-7, 10, and 11) and/or to rejoin process claims once the product claims are found allowable.

Specification Amendments

The specification is amended to capitalize the trademarked term "KNOCK-OUT" at paragraphs [00016] and [00028]. Also, per Examiner's request paragraph [00016] is amended so the term "KNOCK-OUT" is accompanied by the generic terminology. Support for this amendment can be found, for example, at page 4, [00013] of the specification.

Claim Amendments

Claim 8 is amended to delete the language relating to osmolarity from the last element (human embryonic stem cells) and to insert it into the second element describing the nutrient medium. Applicants note this amendment was suggested by the Examiner at page 4 of the present Office Action to improve claim clarity. Support for these amendments is found through out the application, for example, in the embodiments described in pages 4-6. No new matter is added.

Claim Rejections - 35 USC §112

Claims 8, 9 and 12 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite. Specifically, the Examiner asserts that it is not clear whether the claim is drawn to

a composition comprising a plate, a medium, and cells, or to a process for using the same. Accordingly, Claim 8 is amended as suggested by the Examiner to clarify any perceived indefiniteness.

Claim Rejections - 35 USC §103

Claims 8, 9 and 12 are rejected under 35 U.S.C. §103(a) as being unpatentable over Price et al. (2002, U.S. Patent Application Publication 2002/0076747). Specifically, the Examiner asserts that Price et al. teach a composition comprising a culture plate; a nutrient medium (paragraph 128) therein; and mouse embryonic stem cells (ES-D3 cells)(Example 1, paragraphs 129-133). *The Examiner acknowledges that Price et al. do not exemplify a composition having a nutrient medium of 330 or 350 mOsMol or a composition with human ES cells.* However, the Examiner asserts that Price et al. do teach the osmolarity of the medium may be "as high as about 350 mOSMol" (para. 101) and that the medium *may* be used to culture human ES cells (para. 102). Applicants respectfully disagree with the rejection.

Price et al. provide that *"[P]referably, the osmolarity of the 1X medium is between about 280 and 310 mOsmol. However, osmolarity of the 1X medium can be as low as about 260 mOsmol and as high as about 350 mOsmol."* The broad range of osmolarity disclosed in Price et al. does not teach, suggest or motivate one of skill in the art to practice the claimed embodiment. To anticipate or render obvious the present claims, precedent requires that the reference cited by the Patent Office teach with "*sufficient specificity*" a range overlapping or touching the claimed osmolarity. (see, *Atofina v. Great Lakes Chem. Corp,* 441 F.3d 991, 999, 78 USPQ2d 1417, 1423 (Fed. Cir. 2006), wherein when the prior art discloses a range which touches or overlaps the claimed range, but no specific examples falling within the claimed range are disclosed, a case by case determination must be made as to anticipation.) Price et al. teach a broad range without specifying the optimal osmolarity for culturing human ESCs. Likewise, the unexpected results applicants achieved within the range disclosed also render the claims *unobvious*. Selection of osmolarity of the medium is not a routine matter of optimization. Thus, mere suggestion that osmolarity in a mouse ES cell culture medium may be as high 350mOsm does not result in an expectation of success.

Further, applicants submit that the Price et al. disclosure is not enabling. Applicants believe that it would require undue experimentation by one of ordinary skill in the art to determine the optimal osmolarity for human ESCs. Moreover, Price et al. discloses a preferred osmolarity of "between about 280 and 310 mOsmol", which teaches away from applicants' preferred level of osmolarity. In fact, the results displayed in Figs. 3 and 4 of the present application demonstrate that an osmolarity in excess of 330 mOsMol, and preferably an osmolarity of about 350 mOsMol is most efficient for a human embryonic stem cell culture. This result was surprising given that normal human serum has a physiological osmolarity of 290 mOsMol (see page 3, [00012] and page 6 [00038] of the present specification). At best, one skilled in the art might find it obvious to try a higher than preferred osmolarity for culturing mouse ESCs, however, "obvious to try" is not the standard under §103.

In addition, applicants submit that Price et al. do not exemplify a composition having human ESCs. . The passage the Examiner is referring to at page 6 of the current Office Action, provides:

> "[T]he serum-free supplement and the medium of the present invention can be used to culture ES cells derived from a number of animals, including human, monkey, ape, mouse, rat, hamster, rabbit, guinea pig, cow, swine, dog, horse, cat, goat, sheep, bird, reptile, amphibian, and fish." (See [00102] of Price et al.)

One skilled in the art of stem cell related technology recognizes there are clear differences among the broad list of animals recited in Price et al. These differences contribute to variations in the culture conditions for ESCs. To determine an optimal set of conditions for culturing ESCs from a species other than mouse would require undue experimentation on the part of the researcher. Thus, applicants submit that it would not have been obvious, nor simply a matter of routine optimization, to a skilled artisan to substitute mouse ESC culture conditions for human.

Much of the scientific literature relating to stem cells points to differences in culture conditions between mouse and human ESCs. Indeed, applicants have observed that human ESCs have a different optimal osmolarity than other species tested. Specifically, in applicants

hands the rhesus (primate) ESCs prefer a lower osmolarity than human ESCs. Clearly, if monkey and human are so different, there is no reason to expect that mouse and human would be more similar.

To further support the differences in cell culture conditions between mouse and human ESCs, it is submitted that they differ in terms of their requirements for being maintained in an undifferentiated state and their cell surface markers. For example, mouse, but not human ESCs require LIF in the culture media to remain undifferentiated. LIF and other factors that act through the mouse gp130 receptor can substitute for the feeder layer to aid stem cell self-renewal. Human ES cells have no LIF receptor and according to the inventors, providing LIF in primate ES cell culture media does not maintain cells in an undifferentiated state. In contrast, human ES cell self-renewal is facilitated by feeder cells in a medium containing serum or feeder cells in serum-free medium in the presence of bFGF. Mouse ES cells, but not human ES cells, have the SSEA-1 marker. Human ES cells have the following markers not present on mouse ES cells: SSEA-3, SEA-4, TRA-1-60, and TRA-1-81. (See Table C.1 Comparison of Mouse, Monkey, and Human Pluripotent Stem Cells, Appendix C, NIH Resource for Stem Cell Research; enclosed herewith) The skilled person would have no reasonable expectation that methods used in Price et al. to expand mouse ESCs will apply equally to human ESCs based in-part on the differences noted above. In fact, the conditions do vary because the preferred osmolarity for mouse ESCs is between about 280 and 310 mOsMol and applicants claims require an osmolarity in excess of 330 mOsMol. Accordingly, Price et al. do not render the claimed invention obvious.

Furthermore, applicants submit the Examiner has impermissibly used "hindsight" to reject the claims. It appears the Examiner inadvertently used applicants' teaching as a blueprint to look through Price et al. and piece together (somewhat out of context) elements therein to defeat the patentability of the claimed embodiments. This type of examination is unreasonable and prohibited by the MPEP 2142. In view of these remarks, applicants respectfully request reconsideration of this rejection as applied to the rejected claims.

Accordingly, applicants respectfully request that in view of these claim amendments and remarks, the rejection be respectfully reconsidered, withdrawn and that a timely Notice of Allowance be issued in this case.

A separate petition for a one-month extension of time is enclosed so that this response will be considered as timely filed. No other fees are believed due in regard to this submission. If any other fee is due or any other extension of time is required in this or any subsequent response, please consider this to be a petition for the appropriate extension and a request to charge the petition fee to the Deposit Account No. 17 0055.

Respectfully submitted,

Sara D. Vinarov
Reg. No. 48,524
Attorney for Applicants
QUARLES & BRADY LLP
P.O. Box 2113
Madison, WI 53701-2113

TEL (608) 251-5000
FAX (608) 251-9166